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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/606,042	06/29/2000	Kenneth B. Ain	50229-194	7670

7590 12/22/2003

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	24

DATE MAILED: 12/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/606,042	Applicant(s) AIN ET AL.	
	Examiner Karen A Canella	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *20-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *20-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Please note that the examiner assigned to this application has changed.

2. Claims 1-19 have been canceled. Claims 20-24 have been added

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

4. This application contains sequence disclosures on page 11, lines 34 and 35; page 12, lines 2, 6-7, 28, 29, 31, 32 and 35; page 13, lines 1-7, that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

5. Claims 20 and 23 are objected to because of the following informalities: 5-azacytidine is misspelled as 5-azacytodine. Appropriate correction is required.

6. Claims 20-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inducing the re-expression of the human sodium/iodide symporter in a human thyroid carcinoma cell in vitro, does not reasonably provide enablement for a method of treating thyroid cancer comprising inducing the re-expression of the human sodium/iodide symporter in a human thyroid carcinoma cell in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Claim 20 is drawn to a method of inducing the re-expression of sodium-iodide symporter in human thyroid carcinoma cells comprising the administration of 5-azacytidine, sodium butyrate, dimethylsulfoxide, adenosyl-1,8-diamino-3-thiooctane and phenyl acetate. Claim 23 is drawn to a method for restoring iodide transport to a human thyroid carcinoma cell comprising administering an effective amount of 5-azacytidine. Claim 24 is drawn to a method for restoring iodide transport

to a human thyroid carcinoma cell comprising administering an effective amount of difluoromethylornithine or adenosyl-1,8-diamino-3-thiooctane.

The instant claims encompass a method of activating the expression of the sodium-iodide symporter in thyroid carcinoma cells by means of administering to said cell compounds which induced hypomethylation, such as 5-azacytidine, sodium butyrate, dimethylsulfoxide, adenosyl-1,8-diamino-3-thiooctane and phenyl acetate and difluoromethylornithine. The specification teaches that these agents decrease or eliminate the hypermethylation of the sodium-iodide symporter in the thyroid carcinoma cells. thus, the observation that thyroid carcinoma cells are transcribing the sodium-iodide symporter is consistent with the interpretation that said carcinoma cells are more differentiated that the thyroid carcinoma cells not expressing the said symporter. The induction of differentiation of cancer cells is considered a target of cancer research. However, in the instant case, the agents used to induced the differentiation are cytotoxic and nonspecific for cancer cells, as well as nonspecific for the genes which are being hypomethylated. Bender et al (Pharmaceutical Research, 1998, Vol. 15, pp. 175-187) teach that 5-Aza-CR and 5-Aza-CdR reduce genomic DNA methylation levels, these compounds are both cytotoxic and mutagenic both in vitro and in vivo, and suggests that less toxic agents which target DNA methylation for the treatment of cancer (page 180, second column, first full paragraph). Bender et al teach that agents other than 5-Aza-CR and 5-Aza-CdR are known wherein said agents inhibit Ado Met synthesis or Duchy metabolism, but that use of said agents are limited because interference with Ado Met metabolism impacts other cellular methyl-transferees reactions not related to the methylation of DNA which require Ado Met such as sperm dine and spermine synthesis. Bender et al further teach that use of S-adenosylmthionine analogs for the exclusive inhibition of DNA methylation has not been realized because said analogs exhibit non-specific effects on other enzymes such as AdoMet decarboxylase and AdoHcy hydrolase (page 182, first column, first full paragraph). Bender et al conclude that novel agents which inhibit DNA methylation should be developed, wherein said agents are chemically stable and specific for the DNA methyltransferase (page 182, first column, lines 15-18 of the second full paragraph). The teachings of Bender et al are corroborated in the prior art by Thomas et al (Carcinogenesis, 1992, Vol. 13, pp. 1039-1042) who discloses that agents which demethylate DNA , including the claimed 5-aza-cytidine, result in thyroid tumors in mice

(abstract). Hancock et al (Journal of the National Cancer Institute, 1984, Vol. 72, pp. 833-840) disclose that 5-axacytidine increases the incidence of anchorage-independent growth in a breast tumor cell line (lines 18-20 of the abstract). One of skill in the art would conclude that 5-azacytotdine can induce alterations in gene expression consistent with anchorage-independent growth and thus, promote metastasis. Takenaga (International Journal of Cancer, 1984, Vol. 34, pp. 83-89) discloses that treatment of Lewis lung carcinoma cells with dimethylsulfoxide increased the ability of said cells to colonize the lung (abstract). One of skill in the art would conclude that exposure of carcinoma cells to DMSO can alter gene expression to allow for a more invasive phenotype. Carr et al (Cancer Research, 1987, Vol. 47, pp. 4199-4201) disclose that the administration of 5-azacytidine to patients having non-small cell lung carcinoma did not result in therapeutic efficacy and cause a multitude of undesirable clinical toxicities (abstract). Thus, use of said agents in vivo would be unpredictable because the genes which are demethylated or hypomethylated and subsequently expressed cannot be selected. Therefore genes which contribute to the invasive and metastatic phenotypes could be activated, as demonstrated by Hancocke et al (ibid) and Takaenada (ibid).

Further, in order to induce a therapeutic effect in vivo, it would be necessary to maintain the hypomethylated state of the desired genes. Cosgrove et al (Biochimica et Biophysica Acta, 1990, Vol. 1087, pp. 80-86) teaches that cells respond to drug induced alterations in the methylation content of the DNA by inducing overmethylation (lines 9-11). One of skill in the art would conclude that the induction of hypomethylation of the sodium-iodide symporter could be actively reversed in the tumor cell, therefore the beneficial effect of the differentiation would not be persistent. Additionally, Jones (Trends in Genetics, 1999, Vol. 15, pp. 34-37) teaches that there are some exceptions to the general rule that methylation is correlated with transcriptional activity by pointing out genes in which methylation of the transcribed region is correlated with expression rather than transcriptional inactivity (abstract).

Given the teachings of the art which describe agents which act to demethylate DNA as non-specific, cytotoxic, mutagenic, and tumor , metastasis and invasiveness promoting, one of skill in the art would not be able to use the claimed methods to treat cancer in a patient.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308 8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308 3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308 0196.

Karen A. Canella

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
12/15/03